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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/846,985	05/01/2001	Kenneth J. Cool	DETR 112	3901

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EXAMINER	
GALITSKY, NIKOLAI M	

ART UNIT	PAPER NUMBER
1631	4

DATE MAILED: 01/25/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/846,985	COOL, KENNETH J.	
	Examiner	Art Unit	
	Nikolai M Galitsky	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9 October 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION.

The art unit designated for this application has changed. Applicant(s) are hereby informed that future correspondence should be directed to Art Unit 1631.

RESPONSE TO RESTRICTION REQUIREMENT:

As per restriction requirement set forth in the previous Office action dated 09/04/2001, applicant has elected, with traverse, the Group II, claims 17-22 and 26-30. Insofar as applicant has specifically pointed out the reasons supporting the statement of the traversal, applicant election is taken to be with traverse. In response, the restriction requirement is withdrawn due to said traversal argument being persuasive and all claims 1-30 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The expression "electronic hybridization" in claims 1-13, 15-22, and 30, directly or indirectly via dependence, renders the claims indefinite. The expression "electronic hybridization" is not defined in the claims, the specification does not provide a clear definition, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. In the instant case an electronic hybridization machine is capable of performing sequence analysis utilizing two molecules in the electronic

domain that is practical to implement in the chemical domain, for example comparing a protein sequence to a nucleotide sequence in a hybridization-like assay. A machine such as a general-purpose computer system, a hardware device, implements the hybridization reaction. Thus arises a dual meaning of the expression "electronic hybridization". Generally, electronic as applied to nucleic acid manipulation, refers more specifically to the ability of a component device to electrophoretically transport charged entities for hybridization. For example, Heller et al., (US-Pat-No. 5,849,486; Dec 15, 1998) DNA processing and complexity reduction may optionally be performed by a crude DNA selector component, and a restriction fragment selector component both described as electronic processes therein. The final processed target DNA is transported to the analytical component where electronic hybridization analysis is carried out in a microscopic multiplex format. This analytical component device is also referred to as an analytical chip. Therefore, said expression is vague and indefinite as to whether actual chemical or physical hybridization is included or whether "only" virtual or software hybridization is meant thereby.

In claim 27, line 2, the open term "comprising" implies that the structure is chosen from an unlimited set of options. What options are meant beyond those listed in lines 2-5 of claim 27. Applicant can resolve this issue by amending the term "comprising" in said line 2 to "consisting of".

There are no antecedent bases in claim 1 for the phrase in claims 14 and 30 for the phrase " An apparatus", as claimed in claim 1. It is advised that "An apparatus" is defined in claim 7 and claim 26 and that the correct reference may

be made to claim 7 and claim 26, not claim 1, as made in claim 14 and claim 30, accordingly.

Claim 29 recites the limitation "at least one or more parallel channels" in line 2. This limitation is internally conflicting, because parallel channels require at least two channels.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:
A person shall be entitled to a patent unless --
(b) The invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 – 16 and 23 -30 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Rothberg et al., (US5,871,697; February 16, 1999).

Claim 1 is drawn to a method of "...executing an electronic hybridization assay..." without requiring an actual chemical reaction. Also applicant's note on page 3, lines 5-6 of the instant specification "...the electronic hybridization reaction, generally referred to as a sequence analysis..." The reference describes (See Rothberg et al., (US5,871,697; February 16, 1999), in abstract, lines 4-10, "...The methods make use of information on the presence of carefully chosen target subsequences.... to determine a sample sequence," and in abstract, lines 20-24 ..."Computer implemented methods are provided to analyze the experimental results and to determine the sample sequences ..." and in column 19, lines 61-63 "...output comprising said actual signal and said sequences..."

Claims 7-22, and 26-30 are drawn to an apparatus said executing means comprising a computer appliance structure, software, hardware, etc. Rothberg et al., in columns 76-81 describes an apparatus with the analogous structure and illustrated

futures of the general software structure. For example, in column 77, lines 7-10 Rothberg said, "...the computer methods and instrument control interface can be performed on a multiprocessor or several separate but linked processors, such that instrument control methods, computational experimental methods, and the graphical interface methods can be on different processors in any combination or subcombination...", and in column 19, lines 35-45 describes "...programmable apparatus for displaying data... an input/output device, ...output comprising actual signal said sequences, a computer readable memory..., communication medium..., ...processors, etc. Also, in column 20, lines 7-21 Rothberg et al., describes "...apparatus further comprising one or more instrument devices for probing said sample with said recognition means and for generating said actual signals; and a control device operatively coupled to said one or more instrument devices and to said input/output device for controlling the operation of said instrument devices, wherein said user can input control commands for control of said instrument devices and receive output concerning the status of said instrument devices, and optionally wherein one or more of said selecting, inputting, analyzing, and input/output devices are physically collocated with each other, or are physically spaced apart from each other and are connected by a communication medium for exchanges of commands and information". Also in column 70, lines 37-46 noted, ..."It is preferable that this binding be highly specific and reproducible. Each sample or colony, or an array of samples or colonies, is assayed for the contained sequence by determining which of the set of probes recognizes and thus hybridizes to target subsequences in the sample(s) or colony(ies). Each sample is then characterized by a hash code, each bit of which indicates which probes recognized subsequences, or hits, in a particular sample. The

sequence or gene in a sample is determined from the hash code by computer implemented methods".

Claims 2-3, and 23-25 are drawn to " ...the first sequence so that said executing step is optimized". The reference describes, "... methods wherein a predetermined one or more of the nucleotide sequences are of interest, and the information measure optimized is the number of such sequences of interest which generate at least one signal that is not generated by any other nucleotide sequence...". See Rothberg et al., (US5,871,697; February 16, 1999), column 13, lines 35-45. Also, in column 66, lines 29-34 Rothberg noted "...an information measure, for example the number of good sequences, for an experiment, the optimization methods choose target subsequences, and possibly probes, which optimize the chosen measure.", and in same column, in lines 44 – 45 Rothberg continued "...A preferred optimization method is known as simulated annealing". Simulated annealing attempts to find the minimum of an "energy" function of the "state" of a system by generating small changes in the state and accepting such changes according to a probabilistic factor to create a "better" new state. Also in column 56, lines 8-11 Rothberg et al., noted ..."If stringency conditions are such that exact complementarity is not required for hybridization, false positive signals can be generated, that is signals resulting from inexact recognition of the target subsequence".

Claims 4 and 14 are drawn to "...performing correlation algorithm..." The reference describes, "...analysis methods present an easy to use user interface and permit determination of the sequences actually causing a signal in cases where the signal may arise from multiple sequences, and perform statistical correlations to quickly determine signals of interest in multiple samples." (See Rothberg et al., (US5,871,697; February 16, 1999), column 57, lines 65-67, and column 58, lines 1-3.

Claim 5 is drawn to "a method ..... of identifying the first molecule....". The reference describes "... a method for identifying... DNA molecules in a sample of DNA molecules having a plurality of different nucleotide sequences...". (See Rothberg et al., (US5,871,697; February 16, 1999), column 20, lines 54-58.

Claims 12-13 are drawn to an apparatus comprising executing means, which is optimized. The reference in column 18, lines 53-56 describes "...control device optimizes the value of said information measure according to a method comprising simulated annealing, wherein said first control device repeatedly selects further target subsequences...", and in column 40, lines 63-68, "The RE embodiments are generally more accurate, with fewer false positive and negative identifications, since the RE/ligase recognition reaction is generally more specific than the hybridization of PCR primers to their short subsequence targets, even under stringent hybridization conditions".

Claim 29 is drawn to " ...means for correlating including at least or more parallel channels...". The reference describes the same idea to use "... parallelizing signal detection". (See Rothberg et al., (US5,871,697; February 16, 1999), column 4, lines 66-68.

Claim Rejections - 35 USC § 103(a)

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having

ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6 are rejected under 35 U.S.C. § 103(a) as being unpatentable by Ashley (see J.Am.Chem.Soc. 1992, Vol.114, No. 25, pages 9731-9736), taken in view of Rothberg et al., (US5,871,697; February 16, 1999).

Claims 1-6 are drawn to a method of "...executing an electronic hybridization assay..." without requiring an actual chemical reaction. Also applicant note on page 3, lines 5-6 "...the electronic hybridization reaction, generally referred to as a sequence analysis...". Ashley in column 2, page 3732, describes ..."DNA modeling calculations were used to investigate the hybridization between two nucleic acids of opposing chirality. Given the vary large number of possible conformations for the mixed-enantiomer complexes as well as potential inaccuracies in the simplified calculations,...".

Rothberg et al., taken as whole describes the methods make use of information on the presence of carefully chosen target subsequences, typically of length from 4 to 8 base pairs, and preferably the length between target subsequences in a sample DNA sequence together with DNA sequence databases containing lists of sequences likely to be present in the sample to determine a sample sequence. The preferred method uses restriction endonucleases to recognize target subsequences and cut the sample sequence. Then carefully chosen recognition moieties are ligated to the cut fragments, the fragments amplified, and the experimental observation made. Polymerase chain reaction (PCR) is the preferred method of amplification. Another embodiment of the invention uses information on the presence or absence of carefully chosen target subsequences in a single sequence clone together with DNA sequence databases to determine the clone sequence. Computer implemented methods are provided to

analyze the experimental results and to determine the sample sequences in question and to carefully choose target subsequences in order that experiments yield a maximum amount of information.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the apparatus of Rothberg et al., with the method of DNA modeling calculations were used to investigate the hybridization between two nucleic acids of opposing chirality's, as described in Ashley, because Rothberg et al. given suggestion that the computer methods are provided to analyze the experimental results and to determine the sample sequences in question and to carefully choose target sequences in order that experiments yield a maximum amount of information, thus resulting in the practice of the instant invention.

Claims 7-16 are rejected under 35 U.S.C. § 103(a) as being unpatentable by Mitsuhashi et al., (US5,556,749, September 17, 1996), taken in view of Rothberg et al., (US5,871,697; February 16, 1999).

Claims 7-16 are drawn an apparatus, which is a computer appliance structure comprising means for executing electronic hybridization assay.

Mitsuhashi et al., described in column 7, lines 16 – 20, « ...There is disclosed herein a system which allows the user to calculate and design extremely accurate oligonucleodide probes for DNA and mRNA hybridization procedures. The invention runs under Microsoft Windows on IBM compatible computers...." Also, in column 12, lines 66-67, and in column 13, lines 1-5, Mitsuhashi et al., continued, "...The intent of this invention is to provide one or more fast processes for performing exact and inexact matching between DNA sequences... Hybridization strength between a candidates oligonucleotide probe and sequences of DNA, mRNA or cDNA can be estimated through a hybridization strength...".

Rothberg et al., taken as whole describes the methods make use of information on the presence of carefully chosen target subsequences, typically of length from 4 to 8 base pairs, and preferably the length between target subsequences in a sample DNA sequence together with DNA sequence databases containing lists of sequences likely to be present in the sample to determine a sample sequence. The preferred method uses restriction endonucleases to recognize target subsequences and cut the sample sequence. Then carefully chosen recognition moieties are ligated to the cut fragments, the fragments amplified, and the experimental observation made. Polymerase chain reaction (PCR) is the preferred method of amplification. Another embodiment of the invention uses information on the presence or absence of carefully chosen target subsequences in a single sequence clone together with DNA sequence databases to determine the clone sequence. Computer implemented methods are provided to analyze the experimental results and to determine the sample sequences in question and to carefully choose target subsequences in order that experiments yield a maximum amount of information.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the apparatus of Rothberg et al., with the system which allows the user to calculate and design extremely accurate oligonucleodide probes for DNA and mRNA hybridization procedures., as described in Mitsuhashi et al, because Rothberg et al. given suggestion that the computer methods are provided to analyze the experimental results and to determine the sample sequences in question and to carefully choose target sequences in order that experiments yield a maximum amount of information, thus resulting in the practice of the instant invention.

Claims 17-22 are rejected under 35 U.S.C. § 103(a) as being unpatentable by Fodor et al., (US5,295,525, July 20, 1999), taken in view of Rothberg et al., (US5,871,697; February 16, 1999).

Claims 17-22 are drawn to a machine-readable medium having a program of instructions, providing output. Fodor et al., in column 54, lines 50-59 describes "... Data analysis will typically involve aligning the proper sequences with the overlaps to determine the target sequence. The data analysis can be performed by a computer using an appropriate program." Fodor notes in column 55, lines 32-35 "A variety of computer systems may be used to run a sequencing program. The program may be written to provide both the detecting and scanning steps together and will typically be dedicated to a particular scanning apparatus".

Rothberg et al., taken as whole describes the methods make use of information on the presence of carefully chosen target subsequences, typically of length from 4 to 8 base pairs, and preferably the length between target subsequences in a sample DNA sequence together with DNA sequence databases containing lists of sequences likely to be present in the sample to determine a sample sequence. The preferred method uses restriction endonucleases to recognize target subsequences and cut the sample sequence. Then carefully chosen recognition moieties are ligated to the cut fragments, the fragments amplified, and the experimental observation made. Polymerase chain reaction (PCR) is the preferred method of amplification. Another embodiment of the invention uses information on the presence or absence of carefully chosen target subsequences in a single sequence clone together with DNA sequence databases to determine the clone sequence. Computer implemented methods are provided to analyze the experimental results and to determine the sample sequences in question

and to carefully choose target subsequences in order that experiments yield a maximum amount of information.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the apparatus of Rothberg et al., with the program that written to provide both the detecting and scanning steps together and will typically be dedicated to a particular scanning apparatus as described in Fodor et al, because Rothberg et al. given suggestion that the computer methods are provided to analyze the experimental results and to determine the sample sequences in question and to carefully choose target sequences in order that experiments yield a maximum amount of information, thus resulting in the practice of the instant invention.

Claims 23-25 are rejected under 35 U.S.C. § 103(a) as being unpatentable by Mitsuhashi et al at al., (US5,556,749, September 17, 1996), taken in view of Rothberg et al., (US005871697A; February 16, 1999).

Claims 23-25 are drawn to a method of correlating, optimizing a first sequence and a reference sequence.

Mitsuhashi in column 3 lines 20 – 25 describes "... the problem that the researcher faces is to discover or design a probe or mixture of probes that maximizes the researchers chances of successful hybridization while at the same time minimizing the amount of time and money that has to be spent on discovering or designing the probes. Researchers in the field have determined that computer analysis can greatly expedite and simplify the search for optimal probe sequences. However, "...a true optimization of the probe in terms not only of degeneracy but in terms of length, codon usage, Guanine-Cytosine (GC) avoidance, and expected signal-to-noise ratio (hybridization to target over background) is a fairly complex problem, ..."

Rothberg et al., taken as whole describes the methods make use of information on the presence of carefully chosen target subsequences, typically of length from 4 to 8 base pairs, and preferably the length between target subsequences in a sample DNA sequence together with DNA sequence databases containing lists of sequences likely to be present in the sample to determine a sample sequence. The preferred method uses restriction endonucleases to recognize target subsequences and cut the sample sequence. Then carefully chosen recognition moieties are ligated to the cut fragments, the fragments amplified, and the experimental observation made. Polymerase chain reaction (PCR) is the preferred method of amplification. Another embodiment of the invention uses information on the presence or absence of carefully chosen target subsequences in a single sequence clone together with DNA sequence databases to determine the clone sequence. Computer implemented methods are provided to analyze the experimental results and to determine the sample sequences in question and to carefully choose target subsequences in order that experiments yield a maximum amount of information.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the apparatus of Rothberg et al., with the system which allows the user to calculate and design extremely accurate oligonucleodide probes for DNA and mRNA hybridization procedures, as described in Mitsuhashi et al, because Rothberg et al. given suggestion that the computer methods are provided to analyze the experimental results and to determine the sample sequences in question and to carefully choose target sequences in order that experiments yield a maximum amount of information, thus resulting in the practice of the instant invention.

Claims 26-30 are rejected under 35 U.S.C. § 103(a) as being unpatentable by Leibowitz (see US Patent No. 4,660,164, April 21, 1987), taken in view of Rothberg et al., (US005871697A; February 16, 1999).

Claims 26-30 drawn to an apparatus comprising correlating means. Leibowitz in abstract, lines 1-5 describes "...digital correlator device for correlating serial data against reference data. The device includes a plurality of digital correlators configured to operate in parallel ...". Rothberg et al., taken as whole describes the methods make use of information on the presence of carefully chosen target subsequences, typically of length from 4 to 8 base pairs, and preferably the length between target subsequences in a sample DNA sequence together with DNA sequence databases containing lists of sequences likely to be present in the sample to determine a sample sequence. The preferred method uses restriction endonucleases to recognize target subsequences and cut the sample sequence. Then carefully chosen recognition moieties are ligated to the cut fragments, the fragments amplified, and the experimental observation made. Polymerase chain reaction (PCR) is the preferred method of amplification. Another embodiment of the invention uses information on the presence or absence of carefully chosen target subsequences in a single sequence clone together with DNA sequence databases to determine the clone sequence. Computer implemented methods are provided to analyze the experimental results and to determine the sample sequences in question and to carefully choose target subsequences in order that experiments yield a maximum amount of information.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the apparatus of Rothberg et al., with the device includes a plurality of digital correlators configured to operate in parallel, ...as

described in Mitsuhashi et al, because Rothberg et al. given suggestion that the computer methods are provided to analyze the experimental results and to determine the sample sequences in question and to carefully choose target sequences in order that experiments yield a maximum amount of information, thus resulting in the practice of the instant invention.

The disclosure is objected to because of the following informalities:

In the specification on page 3, line 12 the phrase "The greater, the greater..." is confusingly repeated.

Appropriate correction is required.

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR □ 1.6(d)). The CM1 Fax Center number is either (703) 308-4242 or (703) 305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nikolai M Galitsky, Ph.D., whose telephone number is (703) 308-2422. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Bill Phillips, whose telephone number is (703) 305-3482 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

January 14, 2002

ARDIN H. MARSCHEL
PRIMARY EXAMINER